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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/916,045	07/25/2001	Daniel Santi	300622005700	7402
25225	7590	06/01/2004	EXAMINER	
MORRISON & FOERSTER LLP 3811 VALLEY CENTRE DRIVE SUITE 500 SAN DIEGO, CA 92130-2332			KERR, KATHLEEN M	
			ART UNIT	PAPER NUMBER
			1652	

DATE MAILED: 06/01/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/916,045	SANTI ET AL.	
	Examiner	Art Unit	
	Kathleen M Kerr	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
 - If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
 - If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
 - Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 18 March 2004.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-7 and 12-16 is/are pending in the application.
- 4a) Of the above claim(s) 12-16 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-5 is/are rejected.
- 7) ☒ Claim(s) 6 and 7 is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☒ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|---|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

Application Status

41
5/26/04

1. In response to a previous Office action, a non-final ^{rejection} ~~requirement~~ (mailed on August 12, 2003), Applicants filed a response and amendment received on February 12, 2004. Claims 1, 5, and 7 are amended, and Claims 8-11 cancelled. Thus, Claims 1-7 and 12-16 are pending in the instant Office action. Claims 12-16 remain withdrawn from further consideration as non-elected inventions. Thus, Claims 1-7 will be examined herein.

Priority

2. As previously noted, the instant application is granted the benefit of priority for the U.S. Provisional Application No. 60/220,651 filed on July 25, 2000.

Maintained - Objections to the Specification

3. Previous objection to the specification for the following discrepancy is maintained:
- a) -
 - b) "On page 8, the Table at the bottom has bad margins such that "ACP" (see line 26) is inappropriately in the gene column." Applicant indicates that the margins are, in fact, erroneous, yet no substitute page has been provided. Only upon allowance is an Examiner's amendment appropriate, thus, to obviate the instant objection, Applicant must provide such a substitute page.
 - c) -

Clarification and/or correction are required.

Withdrawn - Objections to the Specification

4. Previous rejection to the specification because the title is not descriptive is withdrawn by virtue of Applicant's amendment.
5. Previous objection to the Abstract is objected to for not completely describing the disclosed subject matter is withdrawn by virtue of Applicant's amendment. Although Applicant did not add a description of methods involving inactivation of the epoK gene, an additionally disclosed invention of the instant application, the naming of epoK in the abstract is sufficient.
6. Previous objection to the specification for the following discrepancies is withdrawn by virtue of Applicant's amendment and/or the Examiner's reconsideration in light of Applicant's comments:
 - a) On page 5, line 27, the reference to 09/443,501 must be updated to USPN 6,303,342.
 - b) -
 - c) On pages 33-35, Example 4 is disclosed and includes data on metyrapone included in Figure 1; other data included in Figure 1 is not described experimentally and is, thus, confusing.

Withdrawn - Claim Objections

7. Previous objection to Claim 10 under 37 C.F.R. § 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim is withdrawn by virtue of Applicant's cancellation of said claim.

New – Claim Objections

8. Claims 6 and 7 are objected to from depending from a rejected claim.

Withdrawn - Claim Rejections - 35 U.S.C. § 112

9. Previous rejection of Claims 1-4 and 6-10 under 35 U.S.C. § 112, second paragraph, as being indefinite for the term “epothilone producing microorganism” is withdrawn by virtue of Applicant’s amendment to using *S. cellulosum*.
10. Previous rejection of Claims 1-11 under 35 U.S.C. § 112, second paragraph, as being indefinite for the term “**an** epothilone epoxidase” (emphasis added) is withdrawn by virtue of Applicant’s amendment to “the epoK gene product” which is a single, specific protein endogenous to *S. cellulosum* as described in the specification.
11. Previous rejection of Claim 8 under 35 U.S.C. § 112, second paragraph, as being indefinite is withdrawn by virtue of Applicant’s cancellation of said claim.
12. Previous rejection of Claim 9 under 35 U.S.C. § 112, second paragraph, as being indefinite is withdrawn by virtue of Applicant’s cancellation of said claim.
13. Previous rejection of Claims 7-11 under 35 U.S.C. § 112, first paragraph, enablement, as failing to comply with the enablement requirement, is withdrawn by virtue of Applicant’s cancellation of said claims and the Examiner’s reconsideration with respect to Claim 7 as noted below.

Applicant’s arguments concerning the generalities of P₄₅₀ inhibitors are enlightening and useful to the record. The Examiner agrees that, considering the limited number of P₄₅₀ inhibitors in Claim 7, testing is not considered undue for the determination of which of those compounds listed will inhibit epoK and, thus, be applicable to the claimed method. The Examiner maintains

Art Unit: 1652

that the effect of the listed compounds on cell growth is a *significant* factor in the enablement of the claimed methods. The effect is considered significant because the example taught in the specification using metyrapone shows significant detriment to cell growth (see Figure 2) and because P₄₅₀ inhibitors are known antibacterials (i.e., will kill the fermenting organism *S. cellulosum*). The Examiner reiterates that the specification contains no data specific to the compounds of Claim 7. However, the Examiner has reconsidered her position determining that it is more likely than not (i.e., predictable) that **some** concentration of the listed compounds will inhibit epoK and not yet kill the *S. cellulosum* so as to produce the claimed epotihlone derivatives resulting in a functioning method.

Maintained - Claim Rejections - 35 U.S.C. § 112

14. Previous rejection of Claims 1-5 under 35 U.S.C. § 112, first paragraph, written description, is maintained. The Examiner notes that language similar to that found in Claim 8 has been amended into Claim 5; Claim 8, now cancelled, had been previously rejected under written description. Applicant's arguments have been fully considered but are not deemed persuasive for the following reasons.

Applicant argues that the rejection would have been more proper as a rejection under 35 U.S.C. § 101, for lacking utility in that the claimed invention would not work since the rejection discusses how only one example of the claimed method is "useful"; the Examiner disagrees. While the term "useful" was used on a single occasion in the rejection, Applicant misinterpreted its use. As previously stated, only a single species of the claimed method has been *demonstrated*:

Art Unit: 1652

Claims 1-6 and 8 are rejected under 35 U.S.C. § 112, first paragraph, **written description**,

In the instant specification, a single example of an epothilone epoxidase inhibitor useful in the claimed methods is described, metyrapone (see Example 4). While the specification describes, at length, procedures for assaying for inhibitors of epothilone epoxidase using a purified epoK gene product (pages 20-21) and while the specification proposes numerous compounds as inhibitors, such as P₄₅₀ enzyme inhibitors, acetylenic mechanism-based inhibitors, etc., **still only a single species of the inhibitors is demonstrated. No discussion of the structure of metyrapone and how that structure relates to inhibiting function** is described in the specification. In fact, the structures of the numerous proposed inhibitors and classes of inhibitors do not appear to have structural features in common with metyrapone. Thus, having only a single representative species and no structure/function relationship of how that single species functions to inhibit epothilone epoxidase, the species cannot adequately describe the claimed genus. (emphasis added) (see paper mailed on August 12, 2003)

Applicant argues that the Office has not presented a basis for the written description rejection; however, as reiterated above and expounded on below, the species described does not adequately support the genus claimed. This is the proper basis for a written description rejection under 35 U.S.C. § 112, first paragraph. At its broadest, the invention uses *any* epoK inhibitor; one such inhibitor has been fully described. As previously paraphrased from *Enzo Biochem* (63 USPQ2d 1609 CAFC 2002):

To fully describe a genus, applicants must (1) fully describe at least one species of the claimed genus sufficient to represent said genus whereby a skilled artisan, in view of the prior art, could predict the structure of other species encompassed by the claimed genus and (2) identify the common characteristics of the claimed molecules, e.g., structure, physical and/or chemical characteristics, functional characteristics when coupled with a known or disclosed correlation between function and structure, or a combination of these. (see paper mailed on August 12, 2003)

In the instant case, no combination of structure and function is noted. Even though inhibitors for optional use as epoK inhibitors are described as known P₄₅₀ inhibitors, the mechanism of

Art Unit: 1652

inhibition of metyrapone and epoK is not described so that any relevant structure can be maintained in the claimed genus, which is specific to epoK inhibition. The specification does not describe *which* P₄₅₀ inhibitors are epoK inhibitors or how one of skill in the art would recognize them without experimentation (the bar here is not undue experimentation since the question is one of written description). Without the ability to recognize the genus of inhibitors, one of skill in the art cannot recognize if they are practicing the claimed invention.

Applicant has provided (under Applicant's representative's signature and not in the form of a declaration under 35 U.S.C. § 1.132) a table of apparent K_i values for various inhibitors and epoK. However, such values are more applicable to an enablement rejection. Applicant has incorrectly interpreted the rejection as one asserting inoperativeness; these arguments are irrelevant since the rejection is one of written description as noted above.

Additionally, Applicant notes that the *Lilly* decision is not applicable for the instant rejection; the Examiner disagrees. As noted in *University of Rochester v. Searle* (69 USPQ2d 1886 CAFC 2004), methods of using compounds require a written description of the genus of compounds to be used, wherein analysis of *Lilly* and *Enzo Biochem* must be applied to the compounds used in the claimed methods.

Summary of Pending Issues

15. The following is a summary of the issues pending in the instant application:
- a) The specification stands objected to for improper margins on page 8 in the Table; a substitute Table is required.
 - b) Claims 6-7 are objected to for depending from a rejected claim.
 - c) Claims 1-5 stand rejected under 35 U.S.C. § 112, first paragraph, written description.

Allowable Subject Matter

16. As previously noted, "Claim 6, drawn to methods of making desoxyepothilone by fermentation in the presence of metyrapone is free of the prior art. No prior disclosure of treatment of epothilone-producing microorganisms with this compound is known. While the prior art teaches inactivating the epoK gene recombinantly to produce an epothilone PKS in the absence of an epoxidase function for production of useful epothilones C and D (see particularly USPN 6,303,342), no motivation for using epoxidase inhibitors instead of recombinantly producing this same effect can be found since recombinant means are easier, less detrimental to the overall growth of the host cell, and described so as to be enabled in the prior art, unlike use of epoxidase inhibitors."

17. Claims 6 and 7 stand objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Conclusion

18. Claims 1-5 are rejected; Claims 6-7 are objected to. Applicants must respond to the objections/rejections in each of the numbered sections in this Office action to be fully responsive in prosecution. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See M.P.E.P. § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 C.F.R. § 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO

Art Unit: 1652

MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 C.F.R. § 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kathleen M Kerr whose telephone number is (571) 272-0931. The examiner can normally be reached on Monday through Friday, from 9:00am to 6pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathupura Achutamurthy can be reached on (571) 272-0928. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).



Kathleen M Kerr
Examiner
Art Unit 1652

May 26, 2004